

M. Manuela M. Raposo,^{a*} Ana M. B. A. Sampaio^a and G. Kirsch^b^a Centro de Química, Universidade do Minho, Campus de Gualtar
4710-057 Braga, Portugal^b Laboratoire d'Ingénierie Moléculaire et Biochimie Pharmacologique,
UFR SciFA/Université de Metz, 1, Boulevard Arago, Metz Technopôle,
57078 Metz Cedex 3, France
Received November 3, 2004

A synthesis of 1-alkoxy- and 1-amino- substituted 4-(2-thienyl)-phthalazines is described from halo-derivatives of 4-(2-thienyl)-1-(2*H*)-phthalazinone **3**.

J. Heterocyclic Chem., **42**, 1245 (2005).

Introduction.

The practical interest upon phthalazine derivatives is based on their widespread applications [1-4]. Phthalazines, like others members of the isomeric diazine series, have found wide applications as therapeutic agents [2,5-28]. Phthalazines are also commonly used as ligands in transition metal catalysis, [29-34] as chemiluminescent materials [35-38] and for optical applications [39].

Despite their significance, there are only a limited number of routes for the synthesis of phthalazines. The most commonly employed approach is through *o*-disubstituted benzenes. Thus, condensation of 1,2-diacylbenzenes or their aldehyde counterparts with hydrazine derivatives gives 1,4-disubstituted- or the parent unsubstituted phthalazines, respectively [1-3,5-7,9-10,12,40-47].

Recently, palladium catalyzed coupling reactions were also applied in the phthalazine series [48-49]. Guery *et al* [48] obtained several new phthalazine derivatives through Suzuki coupling.

Due to the nature of the phthalazine nucleus, synthesis of new derivatives becomes an important issue. There has been little reported in the literature concerning 2-thienyl-substituted phthalazines [17-18,50-51].

The synthesis of thienyl- substituted phthalazines **4a**, **6** and **7** was achieved through similar reactions used earlier in the synthesis of phenyl-phthalazines [40-47]. 1-Alkoxy- and 1-amino-phthalazine derivatives were obtained from halo-derivatives **4a-b** of the phthalazinone **3**. Compound **3** was obtained by cyclization of acyl benzoates **2a-b** using hydrazine hydrate. The latter was made through a Friedel-Crafts reaction between thiophene and phthalic acid mono-chloride esters **1a-b**.

Earlier, several authors [46-47] described the synthesis and the evaluation of the biological activity of 1-amino-phthalazines with structure similar to thienyl-phthalazines **7**. These studies showed that the substitution of the phenyl ring in phenyl-phthalazines (or phenyl-pyridazines) by an electron rich heterocycle such as furane or thiophene improve the biological activities for these compounds. Thus, we decide to synthesize several 1-amino-4-thienyl-phthalazines to see if the potential biological activities for these compounds will be improve.

Chlorine, bromine and triflate thienyl-substituted phthalazines **4** and **5** were synthesized in order to be used as precursors on the synthesis of 1-alkoxy- and 1-amino-phthalazines **6-7**. These derivatives could also be used in the future, as coupling components in palladium catalyzed cross-coupling reactions to obtain more complex molecules with potential applications in NLO [52]. For this kind of application the substitution of the phenyl ring by the thiophene ring was already demonstrated to be very important [53].

Results and Discussion

The 2-thienyl-substituted benzoates **2a-b** were obtained in good yields (75-81%), by the standard method of Friedel-Crafts reaction of thiophene with *o*-phthalic acid mono alkyl ester chlorides **1a-b**. These compounds were subsequently cyclized by condensation with hydrazine hydrate to give phthalazinone **3** in 91% yield from benzoate **2a** or in 84% yield from benzoate **2b** (Scheme 1, Table 1). Phthalazinone **3** was already synthesized by Buu-Hoï *et al* [50], by condensation of 2-(2'-thienyl)-2-oxobenzoic acid with hydrazine hydrate.

Bromine, chlorine and triflate substituted phthalazines play an important role in diazine chemistry since they offer the potential for further functionalization. By nucleophilic displacement of the halogen or the triflate groups, numerous otherwise inaccessible diazines become available. To this end we have synthesized and characterized several halo- and triflate phthalazine derivatives.

From **3**, bromo, chloro and triflate derivatives were prepared by reaction respectively with phosphoryl halides and triflic anhydride. The chloride **4a**, bromide **4b**, and triflate **5** were obtained with respectively 87, 94 and 30% yield. 1-Chloro-4-(2'-thienyl)-phthalazine **4a** has been already reported in a patent [51], by condensation of 1,4-dichlorophthalazine with thienyllithium. No data about the derivative are given. The triflate derivative **5** was prepared according to a modified version [54], of the procedure described by Toussaint [55] *et al*. Reaction of **3** with a great excess of the brominating agent gave only the dibromo derivative **4c** in 62% yield. Mass spectrum of **4c** showed the characteristic pattern for a com-

compound with two bromine atoms with molecular ions at m/z 372 (M^+ , $2 \times {}^{81}\text{Br}$, 45), 370 (M^+ , ${}^{79}\text{Br}$ ${}^{81}\text{Br}$, 85) and 368 (M^+ , $2 \times {}^{79}\text{Br}$, 45). The ${}^1\text{H}$ NMR spectrum revealed two doublets: one at δ 7.23 (3'-H) and the other at δ 7.46 (4'-H). On the basis of these data, the 1-bromo-4-(5'-bromo-thieno-2-yl)-phthalazine structure **4c** was assigned to this product (Scheme 1).

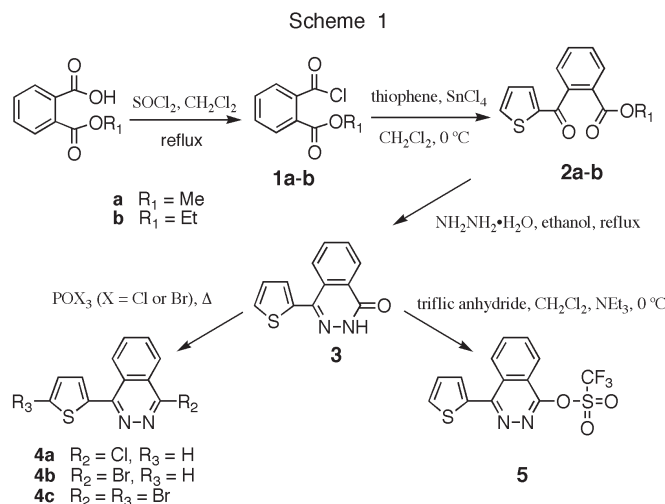


Table 1
Synthesis of Benzoates **2a-b**, Phthalazinone **3** and Phthalazine Derivatives **4a-c** and **5**

Compound	Yield (%)	IR ν_{max} [cm^{-1}]
2a	81	1724 (C=O)
2b	75	1649 (C=O) 1718 (C=O) 1650 (C=O)
3	91	3301 (NH), 1665 (C=O)
4a	99	-----
4b	87	-----
4c	62	-----
5	30	-----

1-Halophthalazines reacted to the alkoxy derivatives **6a-b** when refluxing with the alkoxyde in the corresponding alcohol. Compounds **6a** and **6b**, were obtained in good yields (Scheme 2, Table 2).

Arylamino- and piperidinylphthalazine derivatives show anti thrombotic properties, anti malarial activity and are useful for treatment of septic shock, multi-organ failure, chronic rheumatoid arthritis, multiple sclerosis, SLE, AIDS, hepatitis, type-II diabetes etc. [2,21,47].

In order to synthesize several new 1-(alkyl)arylamino-4-(2'-thienyl)-phthalazines, 1-chloro-4-(2'-thienyl)-phthalazine **4a** was reacted with an excess of piperidine or an excess of several arylamines, in refluxing acetone [56], for

3-15 h, to yield 1-(alkyl)arylamino-4-(2'-thienyl)-phthalazines **7a-e** in moderate to good yields (47-84%) (Scheme 2, Table 2).

It has been reported that 3-hydrazino-6-(2-pyrrolyl)pyridazine can be obtained from the reaction of hydrazine hydrate with 3-chloro-6-(2-pyrrolyl)pyridazine in refluxed *n*-butanol [57]. Using an analogous route, we hoped to prepare 1-hydrazino-4-(2'-thienyl)-phthalazine but we observed that 1-chloro-4-(2'-thienyl)-phthalazine **4a** failed to react with hydrazine hydrate to produce the corresponding phthalazine derivative. In our hands chloro-phthalazine **4a** reacted with hydrazine hydrate in boiling butanol to afford a brown solution from which an orange solid precipitated. The solution revealed to be a mixture of two compounds (tlc). "Flash" chromatography of this mixture on silica with increasing amounts of diethyl ether in light petroleum gave the thienyl-phthalazinone **3** in 87% yield. The second compound eluted was an orange solid, mp 233.7-234.9 °C. Mass spectrum of this compound showed the molecular ion at 452.0880 ($\text{C}_{24}\text{H}_{16}\text{N}_6\text{S}_2$) and an ion at m/z 226 (19%) owing the cleavage into two simple units. The IR spectrum showed one absorption band at 3376 cm^{-1} (NH). ${}^1\text{H}$ NMR spectrum revealed a broad singlet (2H) at 10.65δ due to the NH protons. On the basis of these data, the bis-1,2-[4'-(2''-thienyl)phthalazine-1-yl]-hydrazine structure **8** (8%) was assigned to this product (Scheme 2, Table 2).

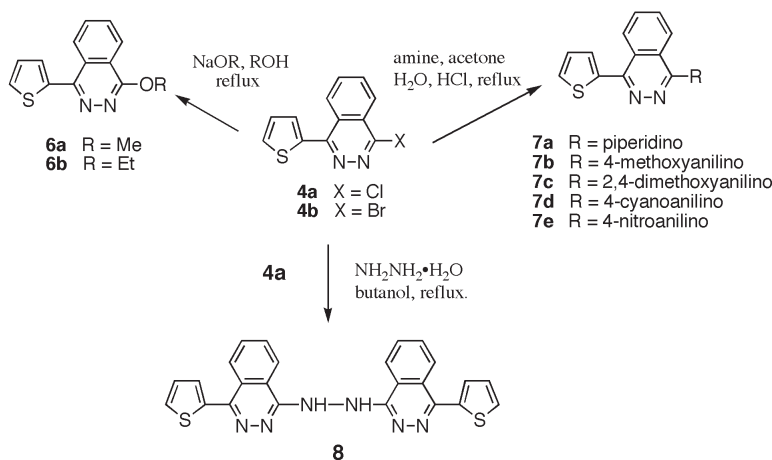
The reaction of **4a** with hydrazine hydrate, under these conditions, gave the oxo derivative **3** in high yield and not the hydrazino derivative, probably due to the hydrolysis of chloro phthalazine **4a** [2,20,58].

Table 2
Synthesis of 1-Alkoxy- and 1-Amino-substituted Phthalazine Derivatives **6a-b**, **7a-e** and Dimmer **8** from 1-Halophthalazine Derivatives **4a-b**

Compound	R	Yield (%)	IR ν_{max} [cm^{-1}]
6a	Me	73	-----
6b	Et	88	-----
7a	Piperidino	84	-----
7b	4-Methoxyanilino	47	3418 (NH)
7c	2,4-Dimethoxyanilino	52	3434 (NH)
7d	4-Cyanoanilino	62	3409 (NH), 2213 (CN)
7e	4-Nitroanilino	71	3281 (NH)
8	-----	9	3376 (NH)

In summary, we report the synthesis of several derivatives of thienyl-substituted phthalazines in order to obtain new derivatives which could exhibit biological activity or in order to be used as precursors on the synthesis of more complex molecules. The examination of biological activity of compounds **7a-e** and **8** are in course.

Scheme 2



EXPERIMENTAL

^1H nmr spectra were obtained on a Varian Unity Plus Spectrometer at 300 MHz and ^{13}C nmr were determined on a Varian Unity Plus Spectrometer at 75.4 MHz using the solvent peak as internal reference. The solvents are indicated in parenthesis before the chemical shift values (δ relative to TMS). Mp's were determined on a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. EI mass spectra EI (70 eV) and hrms were run on a Unicam GC-MS 120. Elemental analysis was carried out on a Leco CHNS-932. Column chromatography was performed on Merck silica gel 60 (Art 9385). Light petroleum refers to solvent boiling in the range 40–60 °C.

General Procedure for the Preparation of Acid chlorides **1a-b**.

The phthalic acid monoalkyl esters (70 mmol) were dissolved in 50 mL of dry dichloromethane and then thionyl chloride (12.5 g, 105 mmol) was added and the mixture was heated at reflux for 4–4.5 h. Evaporation of the solvent under reduced pressure gave the crude acid chlorides **1** which were used without further purification in the Friedel-Crafts reactions.

Phthalic Monoacid Monomethyl Ester Chloride **1a**.

This compound was obtained in quantitative yield as a colorless oil; ^1H nmr (deuteriochloroform) δ 3.87 (s, 3H, OCH_3), 7.60–7.67 (m, 2H, 2xAr-H), 7.75–7.80 (m, 1H, Ar-H), 7.82–7.86 (m, 1H, Ar-H), ir (nujol) ν 2854, 1791 (C=O, acid chloride), 1710 (C=O, ester), 1578, 1488, 1457, 1414, 1386, 1375, 1356, 1343, 1285, 1248, 1181, 1165, 1145, 1128, 1104, 1074, 1037, 995, 826 cm^{-1} .

Phthalic Monoacid Monoethyl Ester Chloride **1b**.

This compound was obtained in 95% yield as a colorless oil; ^1H nmr (deuteriochloroform): δ 1.40 (t, 3H, OCH_2CH_3 , $J = 7.2$ Hz), 4.40 (q, 2H, OCH_2CH_3 , $J = 7.2$ Hz), 7.60–7.65 (m, 2H, 2xAr-H), 7.72–7.76 (m, 1H, Ar-H), 7.84–7.88 (m, 1H, Ar-H), ir (nujol) ν 2860, 1785 (C=O, acid chloride), 1695 (C=O, ester), 1580, 1450, 1465, 1430, 1380, 1360, 1350, 1330, 1230, 1170, 1130, 1096, 1050, 980, 820 cm^{-1} .

General Procedure for the Friedel-Crafts Reaction.

Acid chloride **1** (17.2 g, 114 mmol) and thiophene (9.59 g, 114 mmol/9.03 mL), in dry dichloromethane (200 mL), were added dropwise to a stirred solution of stannic chloride (32.7 g/14.7 mL, 125 mmol,) in dry dichloromethane (200 mL), at 0 °C. After the addition, the mixture was stirred overnight at rt and then poured onto ice-water (1000 mL), acidified with con. HCl and stirred at 0 °C during 1 h. This mixture was extracted with dichloromethane (3x50 mL) and the combined organic extracts were washed with a solution of (5 %) NaOH (3x100 mL), water (2x100 mL) and dried (MgSO_4). Evaporation of the solvent under reduced pressure gave the crude acyl benzoates **2** as oils that were purified by "flash" chromatography on silica with increasing amounts of ether in light petroleum as eluent.

Methyl-2-(thiophene-2-carbonyl)benzoate (**2a**).

This compound was obtained in 81% yield as a colorless solid, mp 67–68 °C; ^1H nmr (deuteriochloroform): δ 3.70 (s, 3H, OCH_3), 7.08 (m, 1H, 4'-H), 7.28 (dd, 1H, 3'-H, $J = 3.5$, 1.2 Hz), 7.50 (dd, 1H, 3 or 6-H, $J = 7.8$, 1.5 Hz), 7.59 (dt, 1H, 4 or 5-H, $J = 7.8$, 1.5 Hz), 7.65 (dt, 1H, 5 or 4-H, $J = 7.8$, 1.5 Hz); 7.71 (dd, 1H, 5'-H, $J = 4.8$, 1.2 Hz), 8.05 (dd, 1H, 6 or 3-H, $J = 7.8$, 1.5 Hz); ir (nujol) ν 3104, 2952, 1724 (C=O, ester), 1649 (C=O, cetone), 1596, 1576, 1515, 1485, 1434, 1412, 1355, 1287, 1321, 1085, 1050, 962, 895, 849, 824, 775, 737, 670, 642 cm^{-1} ; ms: m/z (%) = 246 (M^+ , 92), 215 (36), 187 (7), 163 (100), 111 (100), 76 (40), 69 (20), 57 (58), 50 (75).

Anal. Calcd. for $\text{C}_{13}\text{H}_{10}\text{O}_3\text{S}$: C, 63.42; H, 4.06; S, 13.02. Found: C, 63.38; H, 4.17; S, 13.06.

Ethyl-2-(thiophene-2-carbonyl)benzoate (**2b**).

This compound was obtained in 75% yield as a beige solid, mp 65–67 °C; ^1H nmr (deuteriochloroform): δ 1.14 (t, 3H, OCH_2CH_3 , $J = 6.7$ Hz), 4.15 (q, 2H, OCH_2CH_3 , $J = 6.7$ Hz), 7.08 (m, 1H, 4'-H), 7.28 (dd, 1H, 3-H, $J = 3.7$, 1.2 Hz), 7.49 (dd, 1H, 3 or 6-H, $J = 7.5$, 1.5 Hz); 7.58 (dt, 1H, 4 or 5-H, $J = 7.5$, 1.5 Hz), 7.65 (dt, 1H, 5 or 4-H, $J = 7.5$, 1.5 Hz), 7.71 (dd, 1H, 5'-H, $J = 5.0$, 1.2 Hz), 8.06 (dd, 1H, 6 or 3-H, $J = 7.5$, 1.5 Hz); ir (nujol) ν 3098, 1718 (C=O, ester), 1650 (C=O, cetone), 1595, 1575, 1514, 1411, 1336, 1288, 1132, 1076, 1046, 1040, 1017, 841, 777, 734, 718 cm^{-1} ; ms: m/z (%) = 260 (M^+ , 82), 215 (86), 217 (10), 187 (27), 171 (14), 149 (68), 115 (33), 111 (100), 105 (15), 83 (16), 76 (39), 65 (21), 57 (11), 50 (20).

Anal. Calcd. for $C_{14}H_{12}O_3S$: C, 64.62; H, 4.61; S, 12.32. Found: C, 64.60; H, 4.63; S, 12.44.

Synthesis of 4-(2'-Thienyl)-1-(2H)-phthalazinone (**3**).

A mixture of benzoate **2a-b** (5 g, 20 mmol) and hydrazine hydrate (1.5 g, 30 mmol, 1.45 mL) was heated at reflux in ethanol (35 mL) for 16 h. The mixture was left at -4 °C overnight. After cooling the obtained crystals were collected by filtration and washed with ethanol to give the pure phthalazinone **3** [17-18], [42]. This compound was obtained in 91 % yield from benzoate **2a** and in 84 % yield from benzoate **2b** as colorless needles (ethanol), mp 197-198 °C, (lit. [42] 195 °C); 1H nmr (deuteriochloroform) δ 7.25-7.27 (m, 1H, 4'-H), 7.48 (dd, 1H, 3'-H, J = 3.3, 1.2 Hz), 7.52 (dd, 1H, 5'-H, J = 5.4, 1.2 Hz), 7.80-7.92 (m, 2H, 6 and 7-H), 8.15 (dd, 1H, 5 or 8-H, J = 7.5, 2.4 Hz), 8.54 (dd, 1H, 8 or 5-H, J = 7.5, 2.4 Hz), 10.6 (br. s., 1H, NH); ir (nujol) ν 3301 (NH), 1665 (C=O), 1582, 1431, 1351, 1329, 1229, 1196, 1156, 1083, 1030, 907, 893, 845, 776, 740, 727, 699, 680, 666, 648 cm^{-1} ; ms: m/z (%) = 228 (M^+ , 100), 227 (44), 199 (17), 171 (52), 149 (26), 145 (5), 139 (6), 127 (22), 111 (10), 97 (25), 83 (42), 81 (51); hrms: m/z calc. for $C_{12}H_8N_2OS$: 228.0357; found 228.0352.

Anal. Calcd. for $C_{12}H_8N_2OS$: C, 63.12, H, 3.51, N, 12.27, S, 14.05. Found: C, 63.22, H, 3.67, N, 12.25, S, 14.19.

General Procedure for the Synthesis of 1-Halo-4-(2'-thienyl)-phthalazines **4a-b**.

A mixture of 4-(2-thienyl)-1-(2H)-phthalazinone **3** (1 g, 4.4 mmol), and POX_3 ($X=Cl$ or Br) (8.8 mmol), was heated for 4 h at 110-120 °C. This mixture was cooled till rt and then poured onto ice-water, basified with a solution of ammonia (2 M) and stirred for 15 min. to give a solid which was filtered and washed with water and light petroleum to give the pure 1-halo-4-(2-thienyl)-phthalazines **4a-b**.

1-Chloro-4-(2'-thienyl)-phthalazine (**4a**).

This compound was obtained in 99 % yield as a yellow solid mp 134.5-135.5 °C (ether), (lit. [51] mp not quoted); 1H nmr (deuteriochloroform): δ 7.27-7.30 (m, 1H, 4'-H), 7.64 (dd, 1H, 5'-H, J = 5.3, 1.2 Hz), 7.70 (dd, 1H, 3'-H, J = 3.4, 1.2 Hz), 8.01-8.05 (m, 2H, 6 and 7-H), 8.40 (dd, 1H, 5 or 8-H, J = 8.6, 2.1 Hz), 8.52 (dd, 1H, 8 or 5-H, J = 8.6, 2.1 Hz); ir (nujol) ν 1564, 1529, 1483, 1434, 1374, 1364, 1288, 1263, 1074, 1018, 987, 853, 854, 846, 777, 701, 689, 666 cm^{-1} ; ms: m/z (%) = 248 (M^+ , ^{37}Cl , 37), 246 (M^+ , ^{35}Cl , 100), 228 (17), 211 (72), 182 (16), 139 (25), 109 (10), 91 (6); hrms: m/z calc. for $C_{12}H_7^{37}ClN_2S$: 247.9989; found 247.9989.

Anal. Calcd. for $C_{12}H_7ClN_2S$: C, 58.41; H, 2.83; N, 11.35, S, 13.01. Found: C, 58.60; H, 3.01; N, 11.65; S, 13.35.

1-Bromo-4-(2'-thienyl)-phthalazine (**4b**).

This compound was obtained in 87% yield as a beige solid, mp 177.8-178.2 °C (ethyl acetate). 1H nmr (deuteriochloroform): δ 7.27-7.30 (m, 1H, 4'-H), 7.64 (dd, 1H, 5'-H, J = 5.0, 1.2 Hz), 7.97-8.07 (m, 2H, 6 and 7-H), 8.36 (dd, 1H, 5 or 8-H, J = 8.9, 2.4 Hz), 8.48 (dd, 1H, 8 or 5-H, J = 8.9, 2.4 Hz); ir (nujol) ν 3646, 2923, 1526, 1515, 1432, 1362, 1326, 1278, 1162, 968, 877, 843, 774, 701, 664, 614, 503 cm^{-1} ; ms: m/z (%) = 292 (M^+ , ^{81}Br , 68), 290 (M^+ , ^{79}Br , 73), 228 (9), 211 (100), 182 (8), 139 (36), 113 (6), 102 (17), 91 (12); hrms: m/z calc. for $C_{12}H_7^{79}BrN_2S$: 289.9513; found 289.9515.

Anal. Calcd. for $C_{12}H_7BrN_2S$: C, 49.49; H, 2.40; N, 9.62; S, 11.02. Found: C, 49.47; H, 2.62; N, 9.47; S, 10.88.

Synthesis of 1-Bromo-4-(5'-bromo-thieno-2-yl)-phthalazine (**4c**).

A mixture of 4-(2'-thienyl)-1-(2H)-phthalazinone **3** (1 g, 4.4 mmol), and $POBr_3$ (48.4 mmol), was heated for 4 h at 110-120 °C. This mixture was cooled till rt and then poured onto ice-water, basified with a solution of ammonia (2 M) and stirred for 15 min. to give a beige solid which was filtered and washed with water and light petroleum to give the crude phthalazine **4c** as a beige solid. "Flash" chromatography of this solid with increasing amounts of ether in light petroleum gave the pure dibromophthalazine **5c** in 62% yield as a beige solid, mp 164.0-165.5 °C; 1H nmr (deuteriochloroform): δ 7.23 (d, 1H, 3' or 4'-H, J = 4 Hz), 7.46 (d, 1H, 4' or 3'-H, J = 4 Hz), 8.01-8.05 (m, 2H, 6 and 7-H), 8.35-8.38 (m, 1H, 5 or 8-H), 8.43-8.46 (m, 1H, 8 or 5-H); ir (nujol) ν 3851, 3646, 2924, 1562, 1516, 1434, 1364, 1326, 1278, 1162, 1118, 980, 971, 842, 805, 770, 698, 689, 664, 614, 506 cm^{-1} ; ms: m/z (%) = 372 (M^+ , $2 \times ^{81}Br$, 45), 370 (M^+ , ^{79}Br ^{81}Br , 85), 368 (M^+ , $2 \times ^{79}Br$, 45), 291 (100), 279 (97), 227 (7), 210 (14), 182 (39), 171 (7), 138 (21), 119 (9), 102 (11), 92 (44), 82 (45); hrms: m/z calc. for $C_{12}H_6^{79}Br_2N_2S$: 367.8618; found 367.8620.

Anal. Calcd. for $C_{12}H_6Br_2N_2S$: C, 38.93; H, 1.62; N, 7.57; S, 8.67. Found: C, 39.15; H, 1.92; N, 7.76; S, 8.94.

Synthesis of Trifluoromethanesulfonic Acid [4-(2'-Thienyl)-phthalazine-1-yl] Ester **5**.

Trifluoromethanesulfonic anhydride (0.372 g/0.22 mL, 1.32 mmol), was added slowly dropwise to a stirred ice cooled suspension of phthalazinone **3** (0.2 g, 0.88 mmol) and triethylamine (0.134 g/0.18 mL, 1.32 mmol) in dichloromethane (20 mL). After 12 hours, the mixture was poured into water (30 mL and extracted with dichloromethane (3x50 mL). The combined organic extracts were washed with water (30 mL), dried with $MgSO_4$ and the solvent was evaporated under reduced pressure to give the crude trifluoromethanesulfonic acid [4-(2'-thienyl)-phthalazine-1-yl] ester **5** which was purified by "flash" chromatography on silica with increasing amounts of ether in light petroleum as eluent.

This compound was obtained in 30 % yield as a colorless solid, mp 133.2-134.0 °C. 1H nmr (deuteriochloroform): δ 7.22-7.27 (m, 1H, 4'-H), 7.55 (br. d., 1H, 3'-H, J = 3.6 Hz), 7.60 (br. d., 1H, 5'-H, J = 5.4 Hz), 7.92 (dt, 1H, 6 or 7-H, J = 7.5, 1.2 Hz), 7.98 (dt, 1H, 7 or 6-H, J = 7.5, 1.2 Hz), 8.18 (br. d., 1H, 5-H, J = 8.1 Hz), 8.55 (br. d., 1H, 8-H, J = 8.1 Hz); ^{13}C nmr (deuteriochloroform): δ 30.8, 117.3, 121.6, 127.7, 127.9, 128.6, 129.1, 130.2, 133.2, 134.7, 135.7, 145.2, 158.0; ir (nujol) ν 3851, 3646, 2924, 1714, 1592, 1548, 1428, 1366, 1324, 1281, 1253, 1230, 1197, 1130, 1121, 1086, 1049, 1023, 925, 859, 849, 789, 848, 777, 730, 684, 618, 591, 573 cm^{-1} ; ms: m/z (%) = 360 (M^+ , 41), 199 (100), 228 (17), 171 (45), 127 (12), 85 (6); hrms: m/z calc. for $C_{13}H_7F_3N_2O_3S_2$: 359.9850; found 359.9851.

Anal. Calcd. for $C_{13}H_7F_3N_2O_3S_2$: C, 43.33; H, 1.94; N, 7.78; S, 17.78. Found: C, 43.67; H, 2.23; N, 7.53; S, 17.49.

General Procedure for the Preparation of 1-Alkoxy-4-(2'-thienyl)-phthalazines **6a-b**.

Halophthalazine **4a** was heated at reflux with NaOR ($R=Me$ or Et) in methanol or ethanol (45 mL) for 4 h., and then cooled and the solvent was removed under reduced pressure to give an orange solid. This solid was poured into water (50 mL), and neutralized

with a solution of HCL (10%). The reaction mixture was then extracted with dichloromethane (2x40 mL). The organic extract was dried with MgSO_4 and the solvent was evaporated under reduced pressure to give the crude 1-alkoxy-4-(2-thienyl)-phthalazines **6a-b** which were purified by "flash" chromatography on silica with increasing amounts of ether in light petroleum as eluent.

1-Methoxy-4-(2'-thienyl)-phthalazine (**6a**).

This compound was obtained in 73 % yield as a colorless solid, mp 104.5-105.1 °C; ^1H nmr (deuteriochloroform): δ 4.32 (s, 3H, OCH_3), 7.22-7.27 (m, 1H, 4'-H), 7.55 (dd, 1H, 5'-H, $J = 5.5$, 1.2 Hz), 7.62 (dd, 1H, $J = 3.3$, 1.2 Hz, 3'-H), 7.88-7.91 (m, 2H, 6 and 7-H), 8.30 (dd, 1H, 5 or 8-H, $J = 9.0$, 2.2 Hz), 8.40 (dd, 1H, 8 or 5-H, $J = 9.0$, 2.2 Hz); ^{13}C nmr (deuteriochloroform): δ 54.9, 120.0, 123.3, 125.3, 127.0, 127.3, 127.9, 128.4, 131.7, 132.4, 139.0, 150.5, 159.7; ir (nujol) ν 2923, 1614, 1578, 1541, 1515, 1494, 1433, 1364, 1325, 1278, 1201, 1105, 1051, 969, 852, 843, 786, 774, 701, 686, 664, 615 cm^{-1} ; ms: m/z (%) = 242 (M^+ , 100), 213 (40), 199 (6), 171 (33), 127 (11), 110 (16), 103 (15), 85 (5); hrms: m/z calc. for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{OS}$ 242.0512; found 242.0514.

Anal. Calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{OS}$: C, 64.45; H, 4.13; N, 11.57; S, 13.25. Found: C, 64.49; H, 4.34; N, 11.40; S, 13.21.

1-Ethoxy-4-(2'-thienyl)-phthalazine (**6b**).

This compound was obtained in 88 % yield as a colorless solid, mp 97.9-99.0 °C; ^1H nmr (deuteriochloroform): δ 1.58 (t, 3H, OCH_2CH_3 , $J = 6.9$ Hz), 4.79 (q, 2H, OCH_2CH_3 , $J = 6.9$ Hz), 7.22-7.27 (m, 1H, 4'-H), 7.54 (dd, 1H, 5'-H, $J = 5.0$, 1.0 Hz), 7.61 (1H, dd, 3'-H, $J = 3.6$, 1.0 Hz), 7.87-7.91 (m, 2H, 6 and 7-H), 8.31-8.34 (m, 1H, 8-H), 8.38-8.41 (m, 1H, 5-H); ^{13}C nmr (deuteriochloroform): δ 14.6, 63.4, 120.1, 123.4, 125.3, 127.0, 127.3, 127.8, 128.3, 131.6, 132.3, 139.2, 150.2, 159.4; ir (nujol) ν 2924, 1575, 1536, 1492, 1441, 1413, 1342, 1309, 1166, 1101, 1047, 1024, 927, 877, 774 cm^{-1} ; ms: m/z (%) = 256 (M^+ , 42), 241 (71), 228 (100), 211 (12), 199 (17), 171 (58), 139 (5), 127 (19), 110 (16), 103 (12), 84 (7); hrms: m/z calc. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{OS}$: 256.0670; found 256.0668.

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{OS}$: C, 65.62; H, 4.69; N, 10.94; S, 12.52. Found C, 65.69; H, 4.90; N, 10.50; S, 12.27.

General Procedure for the Synthesis of 1-(Alkyl)arylamino-4-(2'-thienyl)-phthalazines **7a-e**.

Amine (2.43 mmol), water (0.017 mL) and one drop of HCL (37%) were added to a stirred solution of 1-chloro-4-(2'-thienyl)-phthalazine **4a** (4.2 g, 0.81 mmol) in acetone (20 mL). This mixture was heated at reflux for 3-15 h then cooled and the amine chlorohydrate separated by filtration affording a pale brown solution. This organic solution was evaporated under reduced pressure to give a crude solid that was dissolved in dichloromethane and the solution obtained was basified with a solution of ammonia (2 M), extracted with chloroform (3x30 mL) and washed with water (3x30 mL). The combined organic extracts were dried and the solvent was evaporated under reduced pressure to give the crude 1-(alkyl)aryl-4-(2'-thienyl)-phthalazines **7a-e** which were purified by recrystallization or by "flash" chromatography on silica with increasing amounts of ether in light petroleum as eluent.

1-Piperidino-4-(2'-thienyl)-phthalazine (**7a**).

This compound was obtained in a 84% yield as a beige solid, mp 125.3-126.3 °C; ^1H NMR (deuteriochloroform): δ 1.70-1.80 (m, 2H, CH_2), 1.80-2.00 (m, 4H, $2\times\text{CH}_2$), 3.40-3.60 (m, 4H,

$2\times\text{NCH}_2$), 7.20-7.24 (m, 1H, 4'-H), 7.52 (dd, 1H, 5'-H, $J = 4.9$, 1.2 Hz), 7.60 (1H, dd, 3'-H, $J = 3.2$, 1.2 Hz), 7.78-7.80 (m, 2H, 6 and 7-H), 8.08-8.14 (m, 1H, 5 or 8-H), 8.38-8.44 (m, 1H, 8 or 5-H); ^{13}C nmr (deuteriochloroform): δ 24.7, 26.0, 53.4, 121.8, 125.0, 125.9, 126.6, 127.3, 127.7, 128.2, 130.9, 131.5, 139.7, 149.7, 159.9; ir (nujol) ν 1571, 1489, 1438, 1403, 1306, 1288, 1256, 1215, 1150, 1135, 1114, 1041, 1031, 1111, 931, 913, 874, 846, 892, 848, 695 cm^{-1} ; ms: m/z (%) = 295 (M^+ , 53), 294 (20), 266 (38), 252 (7), 239 (21), 227 (8), 213 (40), 196 (10), 171 (16), 129 (6), 110 (16), 103 (15), 84 (100); hrms: m/z calc. for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{S}$: 295.1144; found 295.1144.

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{S}$: C, 69.14; H, 5.76; N, 14.23; S, 10.87. Found: C, 68.90; H, 5.94; N, 13.94; S, 10.92.

1-(4-Methoxyanilino)-4-(2'-thienyl)-phthalazine (**7b**).

This compound was obtained in 47% yield as a yellow solid, mp 140.0-141.0 °C (ether). ^1H nmr (dimethylsulfoxide- d_6): δ 3.76 (s, 3H, OCH_3), 6.86 (d, 2H, 3" and 5" or 2" and 6"-H, $J = 9.0$ Hz), 7.23-7.28 (m, 1H, 4'-H), 7.64 (dd, 1H, 3'-H, $J = 3.6$, 1.0 Hz), 7.72 (dd, 1H, 5'-H, $J = 5.4$, 1.0 Hz), 7.78 (d, 2H, 2" and 6" or 3" and 5"-H, $J = 9.0$ Hz), 7.96-8.06 (m, 2H, 6 and 7-H), 8.32-8.37 (m, 1H, 5 or 8-H), 8.60-8.64 (m, 1H, 8 or 5-H), 9.21 (br. s., 1H, NH); ^{13}C nmr (dimethylsulfoxide- d_6): δ 79.2, 113.6, 118.1, 122.8, 123.3, 124.9, 125.1, 127.6, 127.8, 127.9, 131.7, 132.5, 133.3, 139.6, 146.6, 151.8, 155.0; ir (nujol) ν 3418 (NH), 1616, 1547, 1508, 1382, 1238, 1175, 1032, 838, 768, 708, 646 cm^{-1} ; ms: m/z (%) = 333 (M^+ , 100), 332 (73), 318 (38), 311 (19), 171 (3), 166 (5), 122 (4), 102 (5), 92 (4); hrms: m/z calc. for $\text{C}_{19}\text{H}_{15}\text{N}_3\text{OS}$: 333.0936; found 333.0929.

Anal. Calcd. for $\text{C}_{19}\text{H}_{15}\text{N}_3\text{OS}$: C, 68.45; H, 4.50; N, 12.61; S, 9.63. Found: C, 68.70; H, 4.72; N, 12.83; S, 9.90.

1-(2,4-Dimethoxyanilino)-4-(2'-thienyl)-phthalazine (**7c**).

This compound was obtained in 52% yield as a yellow solid, mp 228.6-229.7 °C (dichloromethane); ^1H nmr (dimethylsulfoxide- d_6): δ 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.70 (dd, 1H, 5"-H, $J = 8.7$, 2.4 Hz), 6.80 (d, 1H, 3"-H, $J = 2.4$ Hz), 7.30-7.36 (m, 1H, 4'-H), 7.39 (d, 1H, 6"-H, $J = 8.7$ Hz), 7.78 (br. d., 1H, 3'-H, $J = 3.6$ Hz), 7.89 (br. d., 1H, 5'-H, $J = 4.8$ Hz), 8.20-8.30 (m, 2H, 6 and 7-H), 8.44-8.91 (m, 1H, 5 or 8-H), 8.89-8.98 (m, 1H, 8 or 5-H), 11.30 (br. s., 1H, NH); ir (nujol) ν 3434 (NH), 1608, 1582, 1507, 1461, 1302, 1207, 1161, 1110, 1024, 890, 842, 816, 784, 759, 662 cm^{-1} ; ms: m/z (%) = 363 (M^+ , 40), 362 (4), 348 (14), 332 (100), 226 (10), 211 (10), 182 (6); hrms: m/z calc. for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$: 363.1041; found 363.1041.

Anal. Calcd. for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$: C, 66.10; H, 4.68; N, 11.57; S, 8.83. Found: C, 66.30; H, 4.90; N, 11.75; S, 9.10.

1-(4-Cyanoanilino)-4-(2'-thienyl)-phthalazine (**7d**).

This compound was obtained in a 62% yield as a colorless solid, mp 247.8-249.2 °C; ^1H nmr (dimethylsulfoxide- d_6): δ 7.26-7.32 (m, 1H, 4'-H), 7.74 (br. d., 1H, 3'-H, $J = 3.3$ Hz), 7.80 (m, 3H, 5', 2" and 6"-H), 8.06 (m, 2H, 6 and 7-H), 8.18 (d, 2H, 3" and 5"-H, $J = 9.3$ Hz), 8.44 (br. d., 1H, 5 or 8-H, $J = 9.0$ Hz), 8.66 (br. d., 1H, 5 or 8-H, $J = 9.0$ Hz), 9.78 (br. s., 1H, NH); ^{13}C nmr (dimethylsulfoxide- d_6): δ 103.0, 118.8, 119.5, 119.9, 123.0, 125.0, 125.4, 128.0, 128.4, 128.8, 132.2, 132.9, 133.1, 139.0, 145.1, 148.5, 151.2; ir (nujol) ν 3409 (NH), 2213 (CN), 1601, 1510, 1442, 1329, 1281, 1245, 1173, 1099, 1045, 925, 837, 781, 737, 625 cm^{-1} ; ms: m/z (%) = 328 (M^+ , 62), 327 (100), 171 (6), 102 (6); hrms: m/z calc. for $\text{C}_{19}\text{H}_{12}\text{N}_4\text{S}$: 328.0783; found 328.0769.

Anal. Calcd. for $C_{19}H_{12}N_4S$: C, 69.50; H, 3.65; N, 17.07; S, 9.77. Found: C, 69.75; H, 3.90; N, 17.32; S, 10.01.

1-(4-Nitroanilino)-4-(2'-thienyl)-phthalazine (**7e**).

This compound was obtained in a 71% yield as a pale yellow solid, mp 226.3–228.3 °C (acetone); 1H nmr (dimethylsulfoxide- d_6): δ 7.31–7.34 (m, 1H, 4'-H), 7.78 (dd, 1H, 3'-H, $J = 3.7, 1.2$ Hz), 7.84 (dd, 1H, 5'-H, $J = 5.6, 1.2$ Hz), 8.06–8.16 (m, 2H, 6 and 7-H), 8.20 (d, 2H, 2" and 6"-H, $J = 9.3$ Hz), 8.30 (d, 2H, 3" and 5"-H, $J = 9.3$ Hz), 8.47 (dd, 1H, 5 or 8-H, $J = 8.4, 1.5$ Hz), 8.73 (dd, 1H, 8 or 5-H, $J = 8.4, 1.5$ Hz), 10.2 (br. s., 1H, NH); ^{13}C nmr (dimethylsulfoxide- d_6): δ 120.5, 121.4, 124.5, 124.9, 126.1, 126.8, 128.3, 130.3, 130.9, 133.8, 134.5, 134.8, 142.4, 145.6, 148.1, 151.6; ir (nujol) ν 3281 (NH), 1608, 1560, 1500, 1379, 1324, 1180, 1105, 854, 782, 748, 712, 649 cm^{-1} ; ms: m/z (%) = 348 (M^+ , 84), 347 (100), 301 (31), 211(8), 171 (6); hrms: m/z calc. for $C_{18}H_{12}N_4O_2S$: 348.0681; found 348.0675.

Anal. Calcd. for $C_{18}H_{12}N_4O_2S$: C, 62.06; H, 3.45; N, 16.09; S, 9.21. Found: C, 62.20; H, 3.81; N, 15.30; S, 9.43.

Synthesis of the Dimmer 1,2-Bis-[4-(thiophene-2-yl)phthalazine-1-yl]-hydrazine (**8**).

A mixture of 1-chlorophthalazine **4a** (0.2 g, 0.8 mmol) and hydrazine hydrate (2.4 mL) in butanol (20 mL) was heated at reflux for 6 h. The mixture was allowed to stand 1 h at rt. After this time an orange solid precipitated. The solid formed, the dimer 1,2-bis-[4-(thiophene-2-yl)phthalazine-1-yl]-hydrazine **8** was separated by filtration and washed several times with ether to afford a pale brown solution. This organic solution was extracted with ethyl acetate (2x30 mL), and the combined organic extracts were washed with water (30 mL) and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave an oil which was purified by "flash" chromatography on silica with increasing amounts of ether in light petroleum as eluent. The first compound eluted was the phthalazinone **3** in a yield of 87% as a pale brown oil. The second component eluted was the dimer **8**. This compound was obtained in a 9% overall yield as an orange solid mp 233.7–234.9 °C (dichloromethane); 1H nmr δ (deuteriochloroform): 7.16–7.20 (m, 2H, 2x4"-H), 7.40–7.48 (m, 4H, 2x (3" and 5"-H)), 7.58–7.70 (m, 4H, 2x (6' and 7'-H)), 7.94 (dd, 2H, 2x (5' or 8'-H), $J = 7.8, 2.1$ Hz), 8.42 (dd, 2H, 2x (8' or 5'-H), $J = 7.8, 2.1$ Hz), 10.65 (br. s., 2H, 2xNH); ir (nujol) ν 3376 (NH), 1611, 1570, 1455, 1390, 1349, 1231, 1192, 1141, 1090, 1031, 923, 849, 797, 769, 701, 666 cm^{-1} ; ms: m/z (%) = 452 (M^+ , 100), 436 (61), 393(7), 226 (19), 211(26), 196 (20), 171 (88), 140 (6), 129 (8), 110 (10), 103 (10), 84 (3); hrms: m/z calc. for $C_{24}H_{16}N_6S_2$: 452.0878; found 452.0880.

Anal. Calcd. for $C_{24}H_{16}N_6S_2$: C, 63.70; H, 3.54; N, 18.58; S, 14.18. Found: C, 63.80; H, 3.81; N, 18.30; S, 14.32.

Acknowledgements.

Thanks are due to Foundation for Science and Technology (Portugal) for financial support through IBQF (UM) and through FEDER, POCTI (ref. POCTI/QUI/37816/2001).

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